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INTERNATIONAL TRENDS AND PATTERNS OF PRIMARY LIVER CANCER

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Primary liver cancer (PLC) is common in many areas of the developing world, but uncommon in most of the developed world. Some evidence suggests, however, that the global pattern of PLC may be changing. To clarify this issue, we examined incidence rates for PLC over the 15-year time period, 1978–92, in selected cancer registries around the world. With some exceptions, developed countries have experienced PLC increases in incidence whereas developing countries have experienced declines. Although the reasons for the trends are not entirely clear, the increased seroprevalence of HCV in the developed world and the elimination of HBV-cofactors in the developing world are likely to have contributed to the patterns. Further progress against PLC may be seen in the developing world once the HBV-vaccinated segment of the population reaches adulthood.
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Key words: *hepatocellular carcinoma; hepatitis B; hepatitis C; aflatoxin B1*

Primary liver cancer (PLC) is the fifth most common cancer in the world[1] and the fourth most common cause of cancer mortality.[2] PLC is composed of several subtypes, including hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, and angiosarcoma. In most countries, hepatocellular carcinoma comprises 85–90% of PLC and so the terms are often used interchangeably.

PLC rates have an extremely wide geographic variation, such that 80% of the cases arise in developing countries, particularly those of southeast Asia and sub-Saharan Africa. Even within a confined geographic area, certain ethnic groups have higher PLC rates than others. In these high-rate populations, chronic infection with hepatitis B virus (HBV), and contamination of foodstuffs with aflatoxin B1 (AFB1) are recognized major risk factors. In contrast, neither HBV nor AFB1 is considered to be a major factor in low-rate areas of the developed world. Alcohol ingestion and, increasingly, hepatitis C virus (HCV) infection are more likely to be related to PLC in these areas. Reports of incidence rates declining in some high-risk populations[3] while increasing in some low-risk populations[4–6] suggest that the global patterns of liver cancer may be changing. To determine whether the reported changes are isolated phenomena or whether new global patterns of liver cancer are emerging, we examined incidence trends over the 15-year period 1978–92.

MATERIAL AND METHODS

Incidence data

To examine the current global pattern of PLC incidence, gender-specific rates in 53 registries were abstracted for 67 populations by Parkin *et al.*[7] An effort was made to include registries from each continent and registries that reported data for more than 1 ethnic group, but no more than 1 registry from any single country was included. To examine the trends over time, gender and age-specific and -standardized incidence rates in 23 populations from 21 registries were retrieved by Parkin *et al.* and *Muir et al.*[7–9] The abstracted rates cover 3 5-year intervals: 1978–82, 1983–87 and 1988–92 and are age-adjusted to the world standard population. Use of a fourth time period (1973–77) was considered but rejected due to its use of the International Classification of Diseases, eighth revision (ICD-8)[10] rather than International Classification of Diseases, ninth revision (ICD-9).[11] The coding for primary liver cancer is not comparable between the eighth and ninth revisions of the ICD, so that comparison of rates can be misleading. Both hepatocellular carcinoma and cholangiocarcinoma are included under the major ICD code for primary liver cancer, 155, so it was impossible to examine the trends for the diagnoses separately.

The criteria used to select registries for inclusion were several. As it was desirable that each country only be represented by 1 registry, the number of years included in *Cancer Incidence in Five Continents* and the comparability of rates from a specific registry with the other registries of that country, were key considerations. Most countries included in the analysis have 5 years of reported data in each time period. If more than 1 registry met the basic criteria, the registry with the highest percentage rate of histologic verification or an upward trend of histologic verification over time was selected. No longitudinal incidence data were available from sub-Saharan African populations.

PLC incidence rates for blacks and whites in the United States were calculated using the SEERStat statistical package.[12] The SEER program is a population-based cancer registry system covering 14% of the U.S. population. Long-term data were available from 9 registries that included approximately 10% of the U.S. population. The SEERStat program was used to adjust the ethnic-specific rates in all time periods to the world standard population.

Data analysis

Percentage changes in incidence rates between 1978–82 and 1988–92 were calculated to show the relative difference in these 2 time periods in each country. In addition, age-specific incidence ratios were computed for each country by dividing the age-specific rates in 1988–92 by those in 1978–82 to assess the changes in rates in various age groups. Figures displaying the incidence trends were prepared using a semi-log scale to facilitate the comparison of temporal trends as well as magnitude; the scale used was such that 1 slope of 10° indicates change of 1% per year.[13]

RESULTS

The age-adjusted incidence rates in males and females for the most recent time period (1988–92), grouped by continent, are shown in Figure 1. As anticipated, the highest rates were evident in southeast Asian and sub-Saharan African populations. Although the highest reported rates in the world were in Khon Kaen, Thailand (male = 97.4, female = 39.0), these rates mainly reflect the exceptionally high incidence of cholangiocarcinoma[14] due to infestation with the liver fluke *Ophisthorchis viverrini*, which is estimated to affect 70% of the population of northeast Thailand.[15] Grouped by continent, the lowest global rates were evident in South and Central America and Oceania. Rates in South American

Abbreviations: AFB1, aflatoxin B1; HBV, hepatitis B vi+rus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGV, hepatitis G virus; TTV, TT virus

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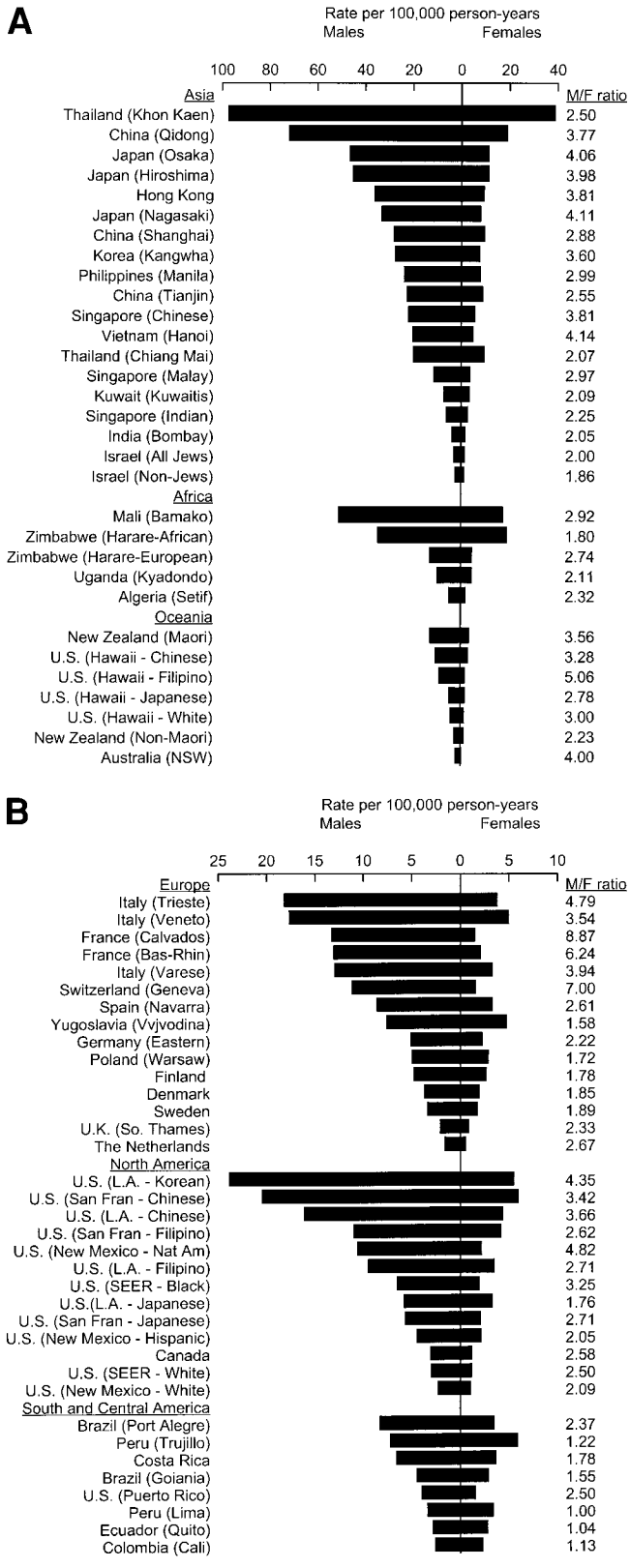

FIGURE 1 – (*a*) Age-adjusted primary liver cancer incidence rates 1988–92: Asia, Africa and Oceania. (*b*) Age-adjusted primary liver cancer incidence rates 1988–92: Europe, North America, South and Central America.

men ranged from 2.6 in Cali, Colombia to 8.3 in Port Alegre, Brazil, whereas rates in South American women ranged from 1.6 in Puerto Rico to 5.9 in Trujillo, Peru. Male rates in Oceania ranged from 2.4 in New South Wales, Australia to 12.8 among the Maori population of New Zealand, whereas female rates ranged from 0.6 in New South Wales to 3.6 among the Maori. Rates in North America and Europe were intermediate to the highest rates reported in Asia and Africa, and the lowest rates in South and Central America, and Oceania. Rates in North American men ranged from 2.3 among the white population of New Mexico to 23.9 among the Korean population of Los Angeles, whereas rates in North American women ranged from 1.1 among the white population of New Mexico to 6.0 among the Chinese population of San Francisco. Rates in European men ranged from 1.6 in the Netherlands to 18.2 in Trieste, Italy, whereas rates in European women ranged from 0.6 in the Netherlands to 5.0 in the Venetian Region of Italy.

In the great majority of registries, male rates were higher than female rates (Fig. 1). Contrary to previous reports,[16] however, the male preponderance tended to be greater in the low-rate countries rather than in the high-rate countries. The highest male:female ratios were seen in the central European registries of Calvados, France (8.8:1), Bas-Rhin, France (6.2:1) and Geneva, Switzerland (7:1). Only in 3 South American registries (Cali, Colombia; Quito, Ecuador; and Lima, Peru) were the ratios at or near 1.

As striking as the international variation are the differences among certain ethnic populations within a single country and among the same ethnic population living in different countries. The variability in ethnic-specific rates within a single country is illustrated by the range of incidence rates in Los Angeles, San Francisco, New Zealand and Singapore**.** As shown in Table I, rates in a single registry can vary as much as 8-fold (White *vs.* Korean male rates in Los Angeles).

The variability in rates of a single ethnic group living in different countries is illustrated by the experience of Chinese and Japanese populations (Figs. 2, 3). Among the Chinese populations, although the rates were higher in China than in the U.S., they were generally 1.5–2 times as high. In contrast, among Japanese populations, the rates in Japan were 5–6 times higher than in U.S. These differences may be due to different temporal periods of immigra-

TABLE I – PRIMARY LIVER CANCER INCIDENCE RATES BY ETHNICITY WITHIN SELECTED REGISTRIES 1988–92

	Male		Female	
	Rate	Rate/ base	Rate	Rate/ base
Los Angeles				
White	2.9[2]	1.00	1.1[2]	1.00
Black	5.1	1.76	2.2	2.00
Japanese	5.8	2.00	3.3	3.00
Hispanic	6.5	2.24	2.2	2.00
Filipino	9.5	3.28	3.5	3.18
Chinese	16.1	5.55	4.4	4.00
Korean	23.9	8.24	5.5	5.00
San Francisco				
White	3.0[2]	1.00	1.2[2]	1.00
Japanese	5.7	1.90	2.1	1.75
Hispanic	6.7	2.23	2.5	2.08
Black	8.1	2.70	2.1	1.75
Filipino	11.0	3.67	4.2	3.50
Chinese	20.5	6.83	6.0	5.00
New Zealand				
Non-Maori	2.9[2]	1.00	1.3[2]	1.00
Maori	12.8	4.41	3.6	2.77
Singapore				
Indian	6.3[2]	1.00	2.8[2]	1.00
Malay	11.6	1.84	3.9	1.39
Chinese	22.1	3.51	5.8	2.07

[1]All rates are age-adjusted to the world standard population and are calculated per 100,000 person-years.–[2]Base rate for comparison in each group.

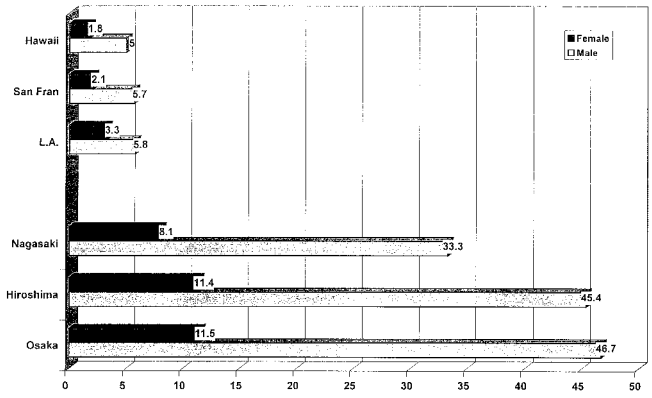

FIGURE 2 – Primary liver cancer incidence among Japanese populations 1988–92.

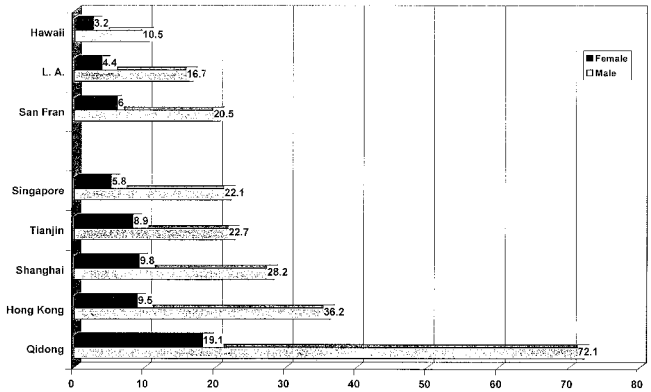

FIGURE 3 – Primary liver cancer incidence among Chinese populations 1988–92.

tion to the U.S. or to differences in risk factors. Hepatitis B virus infection is a significant risk factor among Chinese populations around the world. Among Japanese populations, however, HCV is the dominant risk factor in Japan whereas HBV plays a more significant role in the U.S.[18]

The changes in PLC incidence rates in 22 populations during the intervals 1978–82, 1983–87 and 1988–92 are shown in Figure 4. Among males, the incidence of PLC has increased in populations in Oceania, Central Europe and North America. The largest percentage increases were in New South Wales, Australia, Bas-Rhin, France, Varese, Italy and Alberta, Canada, with overall increases of 108%, 90%, 83% and 70%, respectively. In comparison, the most striking decreases were seen in Asia, particularly among Chinese populations (−30% in Singapore, −18% in Shanghai) as well as in India (−20%), Sweden (−27%) and Zaragoza, Spain (−23%). The changes in female rates resemble the patterns seen in the male rates. Increases were evident in populations of Oceania, Central Europe and North America whereas decreases were most pronounced in Asia, particularly among Chinese populations. In contrast to the increasing rates seen in Central Europe, both male and female rates in Scandinavian populations remained stable at low levels or decreased over time. Similarly, in contrast to stable or decreasing rates in much of Asia, rates in Japan increased markedly over the 15-year time interval. The trends in sub-Saharan African populations could not be examined, as no longitudinal data were available.

In addition to examining age-adjusted rates, age-specific incidence rates were also calculated for the most recent time period (data not shown). Among both males and females, the rates increased with age except in the very oldest age groups. An exception to this pattern is seen in Japan, particularly among males, where the rates plateau at a high level at approximately age 60.

Incidence rate ratios (ratio of incidence in 1988–92 to incidence in 1978–82) were calculated to determine whether the temporal changes in risk affected all age groups equally (data not shown). In those countries where the male rates increased steadily over the 15-year period (Japan, France, Italy, U.S., Canada, Australia and U.K.), the trend affected the great majority of age groups between the ages of 40 and 85+ years. In Japan, France, Italy, Canada and the U.K., however, males between the ages of 55 and 74 experienced larger increases than males in the younger or older age groups. In the U.S. (white, black, Puerto Rican) and Australia, males in the youngest age group (40–44) had similar or greater increases in rates than males in the older age groups. The female rate ratios tended to mirror the male rate ratios, except that females in Australia, Puerto Rico and in the U.S. white population did not experience increases in the youngest age group (40–44). United States black females, however, like U.S. black males, had a disproportionate increase in the youngest age group. Among the populations whose rates steadily declined over the 15-year time interval (Shanghai, Singapore Chinese and Sweden), the decreases were experienced by all but the very oldest age group.

DISCUSSION

The incidence trends of PLC during the period 1978–92 indicate that the global patterns of liver cancer are undergoing substantial change. Although some of the highest risk populations in the world have seen declines in PLC rates, some of the lowest risk populations have experienced steady increases. The male:female incidence ratio is also changing and has become more pronounced in some low-risk populations, where rates have risen more rapidly in males than females.

The underlying explanations for the apparent changes in liver cancer rates are not entirely known. Possible explanations for the trends include: (*i*) changes in screening, diagnosis or coding of hepatocellular carcinoma (HCC); (*ii*) changes in the screening diagnosis or coding of cholangiocarcinoma (CC); (*iii*) changes in the treatment and prognosis of cirrhosis; and (*iv*) changes in the prevalence of the major risk factors for PLC.

To a limited extent, the trends may be related to improvements in the screening, diagnosis or coding of HCC. Large-scale population screening for HCC, however, is not generally practiced in low-risk countries and the principal means of diagnosis, serum alpha-fetoprotein level and ultrasonography, have been in place during most of the 15-year time interval. In addition, HCC was coded by the 9th revision of the International Classification of Diseases throughout the entire interval. Changes in HCC treatment could have affected mortality rates, but great improvements in survival have not been achieved during the period of interest and would not have affected the incidence rates.

In that that both HCC and CC are included under the International Classification of Diseases major code 155 in the 9th revision, it is possible that the changes in PLC rates reflect changes in the rates of CC, rather than of HCC. Although this question can not be examined using the data from *Cancer in Five Continents*, it is possible to examine the trends of HCC and cholangiocarcinoma separately in the U.S. using data from the SEER program. As shown in Figure 5, CC incidence rates in the U.S. have increased in the 15-year time interval for both males and females. Cholangiocarcinoma accounted for 5% of PLC among white males during the 1978–82 time interval but 13% by the 1988–92 interval. Among white females, the percentage of PLC due to CC was 9% in the earliest period and 24% by latest period. Among black males, the percentage of PLC due to CC grew from 4–6% and, in black females, from 3–11%. Although the increased rates of CC are evident in both gender and ethnicity, all 4 groups also experienced increases in the incidence of HCC. The incidence rate of HCC grew 25% in white males, 6.7% in white females, 40% in

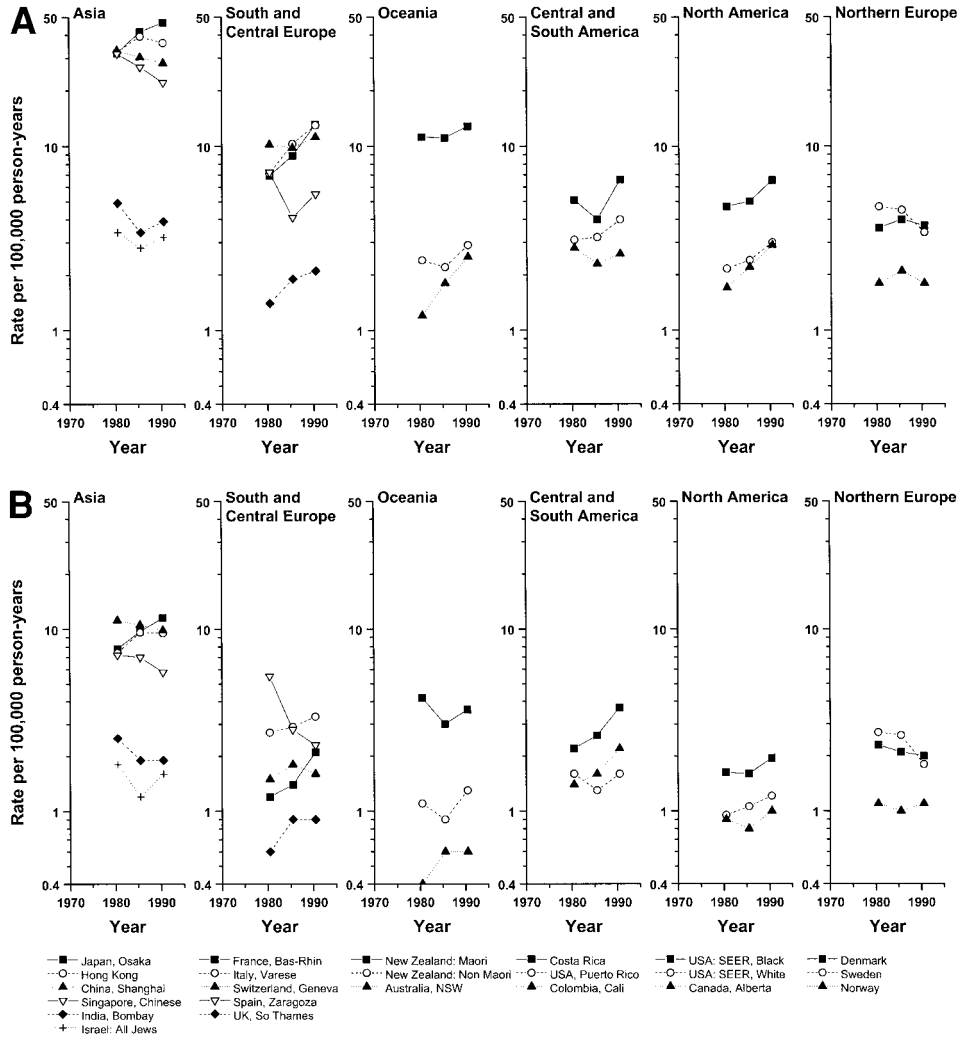

FIGURE 4 – (*a*) Age-adjusted primary liver cancer incidence trends 1978–82 to 1988–92: males. (*b*) Age-adjusted primary liver cancer incidence trends 1978–82 to 1988–92: females.

black males and 13% in black females in the same interval. Given that the incidence rates of HCC are still 3–15 times greater than the incidence rates of CC in these groups, the increases in HCC remain the largest contributor to the increases in PLC in the U.S. Whether the increased rates of CC in the U.S. can be explained by better diagnosis using endoscopic retrograde cholangio-pancreatography[17] better survival of sclerosing cholangitis enabling the development of CC[18] increases in the prevalence of risk factors for CC, or other phenomena, is not yet clear.

Changes in the incidence and mortality rates from cirrhosis may have also affected the rates of PLC given that liver cancers generally arise in cirrhotic livers.[16] Although the evidence suggests that cirrhosis mortality rates have declined in much of the developed world[19] it is likely that the incidence has increased, thereby increasing the prevalence of cirrhosis. The mortality declines may have resulted from declines in alcohol consumption and from the improved survival due to the better care of complications of the disease.[20] The improved survival of cirrhotic patients, however, may have increased the opportunity for the development of HCC in these patients.[21]

The changes in PLC rates may also be due to changes in the prevalence of the major risk factors for HCC. Declining rates in high-risk areas suggest that changes in the major risk factors in those areas, chronic HBV infection and contamination of food-

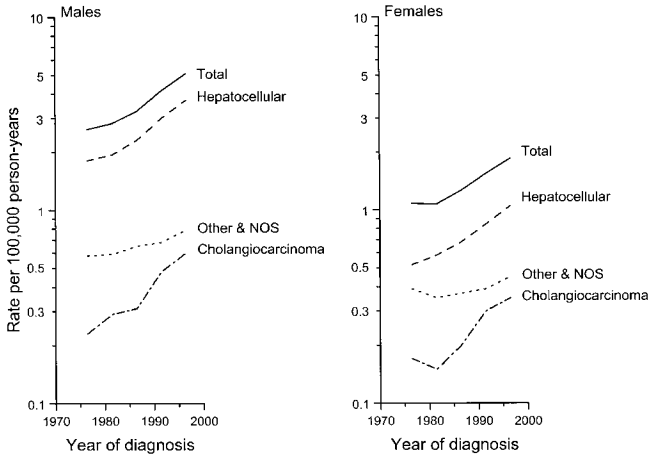

FIGURE 5 – Age-adjusted primary liver cancer incidence trends in the U.S. SEER population by histologic subtype, 1974–78 to 1994–98. All rates are age-adjusted to the world standard population and are calculated per 100,000 person-years. Histology included as HCC, 8170–71; cholangiocarcinoma, 8160–62; other and NOS, all other codes.[85]

stuffs with aflatoxin B1 (AFB1) may be responsible. Although chronic infection with hepatitis B virus has been amply demonstrated to be associated with PLC,[16] infection has been preventable since the licensing of the hepatitis B vaccine in 1982. Studies have demonstrated that the vaccine is 95% effective in preventing chronic HBV infection; however, the cost of the vaccine precludes its availability in many high-risk countries. Whereas most countries of southeast Asia have implemented routine vaccination, most high-risk countries of sub-Saharan Africa have not.[23] The ability of the vaccine to prevent the development of liver cancer in children has now been clearly demonstrated in Taiwan, where a nationwide vaccination program was initiated in 1984.[24] In the first 10 years of the program, the HBsAg carrier rate in children was reduced from 10% to less than 1%[25] and the rate of PLC was halved.[24] Despite such success, however, it is arguably too soon for the HBV vaccine to have affected PLC rates among adults. Most individuals in high-risk countries become chronic HBV carriers as infants or young children, so that vaccinating all age groups in those populations at the present time would have little effect on diminishing the HBV carrier rate among adults. All areas of the world at high risk for PLC, with the exception of Japan, still have HBsAg carrier rates greater than or equal to 8%.[26]

Even though the prevalence of HBV chronic infection in most adult populations is unlikely to have undergone significant change, it is possible that the rate of HBV infection in a country may change due to immigration from HBV endemic areas. For example, during the latter half of the twentieth century, the U.S. experienced an influx of immigrants from many southeast Asian countries. As shown in Table I, the liver cancer rates among individuals of southeast Asian descent have been higher than among other segments of the U.S. population. Whether immigration from HBV endemic areas contributes to the increases in liver cancer seen in the U.S. or in other developed countries, however, is unknown. The increase in rates among both whites and blacks in the U.S. argues that only part of the nationwide increase is related to immigration.

Consumption of foods contaminated with aflatoxin B1 has been a risk factor second only to hepatitis B in high-risk regions. Studies in China have demonstrated that HBV and AFB1 have a synergistic effect on PLC risk.[27–29] Recent efforts in high-risk areas of China to combat aflatoxin contamination[30] seem to have resulted in the declines in PLC incidence. Other public health measures in high-risk areas, such as the removal of Cyanobacteria from water sources,[31,32] may have also contributed to the decreases in PLC rates. Neither AFB1 eradication nor drinking water clean-up, however, would explain why male rates seem to be decreasing more than female rates.

In low-rate areas of the world, hepatitis C virus (HCV) infection and alcohol consumption are more likely to be associated with PLC than are HBV infection and AFB1. Serologic evidence suggests that widespread infection with hepatitis C virus did not occur in most populations until after the Second World War. A notable exception may be Egypt where recent studies suggest that widespread HCV infection resulted from parenteral antischistosomal therapy that was widely used between the 1920s and 1980s.[33] Intravenous drug abuse, blood transfusions and parenteral administration of medications may have facilitated the movement of HCV into the blood supply of developed countries such as Japan, Italy, France and the U.S. Since 1991, however, the blood supplies of most developed nations have been free of HCV and the incidence of post-transfusion hepatitis has dropped accordingly.[34] The main route of transmission now in developed countries is injection drug use.[35] The WHO estimates that approximately 170 million persons are infected and that between 1 and 5% of infected individuals will develop PLC.[36] The reported attributable risk of HCV in PLC varies widely among countries and even among studies within a single country. In Japan, it has been estimated that 60–80% of PLC is related to HCV.[37–41] In Italy, the prevalence of HCV-associated PLC is reported between 40–71%[42–45] whereas in France, the comparable figures are between 27–58%.[44,46] Reports from Spain suggest that HCV is a factor in 60–75% of PLCs[40,44,47] whereas in Germany, HCV may be involved in 26–53% of PLCs.[44,48,49] In Sweden, a country with a low and stable rate of PLC, the percentage of PLC associated with HCV has been reported between 11–37%.[50–52] In China, where the PLC rates are on the decline, the percentage of PLC associated with HCV is between 0–38%.[53–56] In Singapore the comparable figure is between 9–36%[53,54] and in Thailand approximately 17%.[59] In the U.S., the rate of HCV-related tumors is reported between 32–40%.[40,60,61] The risk of developing PLC among HCV-infected individuals, however, is still uncertain as several recent studies have reported few adverse outcomes among populations followed over long periods.[62]

Although the association of HCV with PLC has been convincingly demonstrated, there are likely to be co-factors that modify the risk of HCV-related tumors. The WHO estimates of the anti-HCV seropositivity among various populations do not correlate well with the mortality rates of PLC.[36]. For example, although the male PLC mortality has increased in both France and Italy over time, the 1988–92 rate is lower in France (10.1) than in Italy (12.9), yet the HCV seroprevalence is estimated to be twice as high in France (1.1%) as in Italy (0.5). Similarly, the PLC mortality rate in the 1988–92 period among the U.S. white male population (2.9) is similar to the rate in the Canadian male population (3.2), yet the HCV prevalence rate among the U.S. white population (1.5%) (63) is 15 times higher than that of Canada (0.1%). Some of the discrepancy may be due to small or unrepresentative samples used in estimating seroprevalence in the entire population. Comparisons within a single country, however, indicate that the HCV-PLC relationship may be influenced by other risk factors. A seroprevalence study conducted in 29 centers in Italy found that the rate of HCV infection in the general population did not differ greatly between northern and southern Italy. The percentage of HCV(+) PLC cases was significantly greater in the south (73%), however, than in the north (59%).[64]

Among the factors that may modify the risk of HCV-related PLC are gender, age at infection, concomitant HBV infection, concomitant HIV infection, alcohol consumption and cigarette smoking. A number of studies have reported that male gender, HIV-positivity, HBsAg-positivity and consumption of alcohol increase the risk of PLC among HCV(+) individuals.[45,65–68] Heavy cigarette smoking has also been implicated as a co-factor in some, but not all, studies.[65] The effect of age of infection on PLC risk remains uncertain, with some studies indicating the risk to be greater among persons under age 50[66] and others reporting greater risk among persons of age 40 years or greater.[69–71]. Among these co-factors, the 1 that may have the most significance at the population level is alcohol consumption. Although males are more likely to be infected with both HIV and HBV than are females, the rates of infection in the population are relatively low in comparison with the prevalence rates of alcohol consumption.

Hepatitis G virus (GBV-C, HGV), identified in 1996[72] and TT virus (TTV), identified in 1997[73] have also been examined for a relationship with PLC. Although HGB was significantly associated with PLC in some studies,[56,74] others have reported little if any association.[40,44,55,75–78] TTV has been examined in a number of studies, but no significant association with PLC has yet been reported.[79–84]

In summary, the incidence and mortality patterns of PLC in the world are undergoing significant change, with rates increasing in the developed world and decreasing in some areas of the developing world. Although the PLC increases are a cause of concern, there are some reasons for optimism in the long term. The increased rates in westernized countries are likely to be due to increases in the prevalence of HCV. Although there is no vaccine at the present time, the population seroprevalence of HCV is likely to decline over time. HCV is no longer in the blood supply in these areas of the world and is not easily transmitted sexually or mater-

nally. Given the increasingly limited number of transmission possibilities, HCV infection may become confined to a small proportion of the population, particularly individuals who use injection drugs. Furthermore, in the developing world that has increasing access to the HBV vaccine, a greatly reduced rate of PLC can be anticipated in the long term, whereas in the short term, elimination of cofactors (*e.g.*, AFB1 contaminated foodstuffs) should lead to continuing declines in incidence and mortality.

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